IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Jensenius et al.
Serial No.: 09/874,198
Filed: 4 Jun 2001

Examiner: Moore, William W.
Art Unit: 1652
Attorney's docket: JENSENIUS=3A

Title: MASP-2, a complement-fixing enzyme and uses for it

#13

DECLARATION OF PROF. JENS CHRISTIAN JENSENIUS, D. Phil., Dr. med. AND OF ASS. PROF. STEFFEN THIEL, Ph.D. UNDER 37 C.F.R. § 1.132

I, Professor Jens Christian Jensenius, declare and state as follows:

1. I am employed as Professor of Immunology in the Department of Medical Microbiology and Immunology at the University of Aarhus, Denmark

2. I am co-inventor of the above-identified U.S. application. I have reviewed the Office Action of 28 January 2003.

I, Steffen Thiel, declare and state as follows:

3. I am employed as associate professor of Immunology in the Department of Medical Microbiology and Immunology at the University of Aarhus, Denmark

4. I am co-inventor of the above-identified U.S. application. I have reviewed the Office Action of 28 January 2003.

5. Regarding claims 22 and 28, examiner states that the specification does not disclose treatment of a specific medical condition. However, the specification describes treatment of patients deficient if MASP-2 activity (p. 6, l., 7-8). Deficiency of MASP-2 activity is indeed a medical condition and below a case report of a patient identified by us and collaborators, deficient in MASP-2 activity is described.

   NN, male, born in 1967. In 1996 he developed erythema multiform bullosum with a typical clinical appearance and verified by cutaneous biopsy. Due to a diagnosis of systemic lupus erythematosus (SLE) he was treated with prednisolone later in combination with other immunosuppressive drugs. During this period NN had recurrent herpes infections and recurrent severe lung infections with pneumonia that is often occurring in relation to a immunosuppressive treatment. Progressive lung fibrosis, without vasculitis, alveolitis, or granulomas, was diagnosed in 1997. NN had lost weight, felt tired and complained for dyspnoea, arthralgia, myalgia.

   At the present NN is diagnosed for erythema multiform bullosum, arthralgia and myalgia, relative lymphocytopenia and has slightly elevated C-reactive protein. The immunosuppressive treatment has been limited to a low dosage of prednisolone 5-15 mg daily. Analysis of NN's blood does not reveal any abnormalities in leukocyte number or function. NN has not recently has any severe bacterial infection.

   Serum samples were obtained from the patient and from control individuals. Evaluations of the immune system of the patient show no other serious abnormalities than a compromised MBL pathway.

Analysis by Western blotting showed th presence of MASP-2 in samples of the patient serum. However, th amount of MASP-2 was estimated to be l ss than 10 percent of the amount present in samples of serum from six control individuals.

Analyses of the functional activity of the MBL-MASP complex s by TRIFMA showed sev re deficiency in th MBL pathway activity despite of th MBL l v l being 0.7 µg/ml. Activity of th MBL pathway, expressed in relation to the MBL level showed a value below 10 mU/µg MBL. The 5th to 95th percentile is 300 - 950 mU/µg MBL. As a control of activity of the patient MBL, MASP from MBL deficient serum collected from healthy individuals was used and showed full activity of the patient MBL. Restoration of the MBL pathway was also achieved by adding recombinant MASP-2 to the patient serum. Hence, patient NN suffers from MASP-2 activity deficiency.

6. Regarding claims 47 to 55 it is common within the art to prepare mutants of polypeptides with similar function. Functional MASP-2 mutants are known. In GenBank two different codons for the amino acid at position 371 of MASP-2, i.e., in the first part of the CCP2 domain are found namely: GAT encoding aspartic acid and TAT encoding tyrosine. In a study performed by us and collaborators, out of 15 unrelated control individuals 10 were homozygous for TAT, 3 were heterozygous TAT/GAT, and 2 homozygous for GAT. Hence these variants represent common allotypes of no discernible consequence for the function of MASP-2.

7. We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 27/5 2003

Signature: _____

(Prof. Jens Christian Jensenius)

Signature: _____

(Ass. Prof. Steffen Thiel)